Copy:
Dr. Cattell
Dr. Bing
Dr. Jacobson

PHARMACOLOGY

No. 894

THE COUNCIL FOR TOBACCO RESEARCH - U.S.A., INC.
110 EAST 59TH STREET
NEW YORK, N. Y. 10022

DEC 15 1972

Application For Research Grant

Date: December 5, 1972

1. Name of Investigator(s): (Include Title and Degrees)
Luigi VALZELLI, Prof., M.D., Chief Section Neuropsychopharmacol. (Director of project,
Emilio MUSSINI, Prof., M.D., Chief Section Biochem. Pharmacol. Principal Investigator)
(Research associate)

2. Institution & Address:
Istituto di Ricerche Farmacologiche Mario Negri, Via Eritrea 62 - 20157 Milano, Italy

3. Short Title of Project:
NICOTINE EFFECTS UPON AGGRESSIVE BEHAVIOR

4. Proposed Starting Date: July 1, 1973

5. Anticipated Duration of this Specific Study: 2 years

6. Brief Description of Objectives or Specific Aims:

Prolonged isolation in mice has been widely described as a means for inducing strongly aggressive behavior. This experimental situation was recently defined as the "isolation syndrome" because such animals show several neurochemical as well as behavioral alterations and a difference in response to many centrally acting drugs as compared with normal animals. Preliminary experiments have indicated a differential effect of nicotine in aggressive versus non-aggressive mice, (i.e., attenuation of aggressive behavior in "aggressive mice" and induction of hyperresponsivity and "aggressive" behavior in previously "non-aggressive" animals). The animals which show an experimentally-induced "isolation syndrome" show impaired learning ability and learning disturbances and also show alterations in such behavior when treated with Nicotine. The specific aims of the present research concern experiments in which the pharmacological, biochemical and behavioral parameters of Nicotine-altered behavior interactions are explored. Specially the experiments will be addressed to the issue of defining Nicotine-related changes in the biochemical modifications associated with experimentally-induced abnormalities of behavior. The correlated changes in quantified aggressive behavior would, of course, represent an integral portion of such studies.

7. Give a Brief Statement of your Working Hypothesis:
It is expected that nicotine would act differentially in normal and isolated animals due to differences in the emotional baseline upon which it acts, and which may involve differences in metabolic rate and brain level of this drug. Such indication could also be relevant for a better understanding of the activity of Nicotine in healthy and mentally disturbed men.

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8. *Details of Experimental Design and Procedures: (Attach Separate Pages)*

SEE ENCLOSURE A

9. Physical Facilities Available (Where Other than Administering Organization Indicate Geographical Location)

SEE ENCLOSURE B

10. Additional Requirements:

11. Biographical sketches of all principal and professional personnel (append)

SEE ENCLOSURES C AND D

12. List of publications: (Five most recent as pertinent) (append)

SEE ENCLOSURE E and reprints attached.

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13. Budget: (1st year) $21,748.00

A. Salaries (Personnel by names)	% time	Amount
Professional		
L. VALZELLI (Dir. of Project, Principal Invest.)	25	--
E. MUSSINI (Research Associate)	25	--
(1) Research Assistant	25	REDACTED
(1) Secretary	25	
Technical		
(2) Technicians	50 each	R
	Sub-Total	13,000.00
B. Consumable Supplies (list by categories)	13,000.00	
Animals: cost of purchasing and care		1,500.00
Glassware, Chemicals, Reagents and Drugs		800.00
	Sub-Total	2,300.00
C. Other Expenses (itemize)	15,300.00	
1 or 2 trips a year to U.S.A. for Federation Meetings (April) and Soc. Neurosciences Meeting (October)		1,500.00
Local travel for National and European conferences and congresses		500.00
	Sub-Total	2,000.00
D. Permanent Equipment (itemize)	17,300.00	
(1) Shuttle-box for rats (Basile, Italy)		433.00
(1) Animex S for animal spontaneous locomotor activity (Farad, Sweden)		2,420.00
		2,853.00
E. Overhead (15% of A+B+C)	20,153.00	1,595.00 2595
	Total	21,748.00 22,748

Estimated Future Requirements:

	Salaries	Consumable Suppl.	Other Expenses	Permanent Equip.	Overhead	Total
Year 2	R	2,500.00	2,000.00		1,625.00	19,125.00
Year 3						

It is understood that the applicant and institutional officers in applying for a grant have read and found acceptable the Council's "Statement of Policy Containing Conditions and Terms Under Which Project Grants Are Made."

Signature Luigi Valzelli
Director of Project

Telephone

Signature
Business Officer of the Institution

Telephone

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Other Sources of Financial Support

List financial support for research from all sources, including own institution, for this and/or related research projects.

	Title of Project	Source	Amount	Duration
Current				
Pending				

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ENCLOSURE A

8. DETAILS OF EXPERIMENTAL DESIGN

Among the manifold aspects of the "isolation syndrome" in rodents, there are at least three main behavioral alterations; these consist of a) aggressive behavior, b) alterations in the learning and memory process with impairment, and c) reduction in exploratory behavior.

Moreover, isolated animals develop several differences in brain neurochemistry, principally involving brain serotonin turnover and brain N-acetyl-aspartic acid content, which may to some extent account for the alterations in behavior induced by prolonged isolation.

Based upon a series of previous experimental findings indicating that the response of such animals to centrally acting drugs is profoundly modified, as compared with normal, a series of experiments are proposed wherein the effects of nicotine are considered with regard to:

A) general behavior of normal and isolated mice;

B) aggressive behavior;

C) learning and memory processes in isolated versus normal mice;

D) exploratory behavior of isolated-aggressive mice;

E) spontaneous locomotor activity of normal and aggressive mice;

F) levels and turnover of brain monoamines (serotonin, norepinephrine, dopamine) in normal and isolated-aggressive mice;

G) brain N-acetyl-aspartic acid levels;

H) the relationship between nicotine levels (and possibly of its metabolites) in the brain of normal and aggressive animals.

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In order to determine the extent to which the monoaminergic pathways may be selectively involved in the central effects of nicotine, the activity of this drug will be studied both in normal and isolated aggressive mice previously subjected to stereotaxically or chemically placed lesions of the serotoninergic or catecholaminergic systems.

The above designed experiments will be performed also in normal or isolated rats.

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PROCEDURES

1) Exploratory behavior in mice = hole-board test (Boissier J.R., Simon P., Lwoff J.M., Thérapie, 19, 571, 1964; Valzelli L., Psychopharmacologia, 15, 232, 1969).

2) Avoidance learning = shuttle-box.

3) Aggressive behavior = by prolonged isolation according to the method of Yen et al. (Yen C.Y., Stanger R.L., Millman N., Arch. int. Pharmacodyn. 123, 179, 1959), scored by Valzelli (Valzelli L., Advances in Pharmacology, vol. 5, pp. 79-108, 1967).

4) Spontaneous locomotor activity = measured by an automatized apparatus, ANIMEX S (FARAD, Sweden)

5) Brain monoamine extraction:

a) norepinephrine (NE) and dopamine (DA) according to the method described by Shore and Olin (J. Pharmacol. exp. Ther. 122, 295, 1958) modified by Chang (Int. J. Neuropharmac. 3, 643, 1964) and by Laverty and Taylor (Anal. Biochem. 22, 269, 1968).

b) serotonin (5-hydroxytryptamine = 5HT) and 5-hydroxyindbleacetic acid (5HIAA) simultaneously determined in the same brain tissue sample, according to Giacalone and Valzelli (Pharmacology 2, 171, 1969).

6) Brain monoamines detection and measurement = by an Aminco Bowman spectrophotofluorometric apparatus.

7) Brain amonoamine turnover calculated according to Tozer et al. (Tozer T.N., Neff N.H., Bordie B.B., J. Pharmac. exp. Ther. 153, 177, 1966).

8) N-acetyl-aspartic acid = gas chromatographically determined according to Marcucci and Mussini (J. Chromatogr. 25, 11, 1966).

9) Brain nicotine and its metabolite levels = by gas chromatographic micromethods.

10) Lesions and stimulations of monoaminergic pathways = stereotaxically performed according to Dahlström and Fuxe (Acta Physiol. Scand. 64, suppl. 247, 1965) using the coordinates given by König and Klippel (The rat brain, a stereotaxic atlas of the forebrain and lower parts of the brain, Williams and Wilkins, Baltimore, 1963).

11) Chemical lesions = by 6-hydroxydopamine intraventricularly injected according to Noble et al. (Noble E.P., Wurtman R.J., Axelrod J., Life Sci. 6, 281, 1967) for the catecholaminergic system, and by 5,6-hydroxytryptamine intraventricularly injected according to Haley and McCornick (Br. J. Pharmac. 12, 12, 1957) for the serotoninergic system.

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ENCLOSURE B

9. PHYSICAL FACILITIES AVAILABLE

American Instrument Co. Mod. Aminco-Bowman spectrofluorometers with Moseley Mod. Autograf recorder; Basile automatic conditioned reflex apparatus (shuttle-box); Stoelting stereotaxic apparatus for rats adaptible to mice; Beckman GMBH Mod. DU-G-2400 spectrophotometer; Elvi Mod 670 spectrophotometer; Tektronix Iscilloscope Mod. 502A; Automatized hole-board for exploratory activity (LP Italiana); Grass S-4 electronic stimulator; Beckman Mod 151 microspectrophotometer, Technicon autoanalyzer; Beckman-Spinco Mod. L. ultracentrifuge (50.000 rpm); Ivan Sorvall super-centrifuge; Carlo Erba Fractovap Mod C. gas chromatography units and one with electron capture detector; Carlo Erba Fractovap Mod. G-B gas chromatography unit; Radiometer Mod. Tritator with Tritigraph LKB RadiRac, column chromatography apparatus. Gibertini balances; thermostatic baths, shakers, mechanical and magnetic mixers, centrifuges, Basile recording thermoneters, automatic syringes, Autospense Warner Chilcott automatic pipetters, calculators, homogenizers,; Reichert, Galileo, Leitz and Zeiss microscopes; Elvi and Beckman pH meters; Olivetti Program 101, desk computer.

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ENCLOSURE (C)

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Prof. LUIGI VALZELLI

CURRICULUM VITAE

October 1972

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1. BIOGRAPHICAL SKETCHES

Name = VALZELLI Luigi

Present Position = Chief, Section of Neuropsychopharmacology and Psychophysiology of the Intitute for Pharmacological Research "Mario Negri", Milano, Italy

REDACTED

Student, Faculty of Medicine and Surgery, University of Milan

Internal student, Institute of Normal Human Anatomy and Histology

Internal student, Institute of Pathological Human Anatomy and Histology

Internal student, Institute of Clinical Medicine

November 17th, graduated in Medicine and Surgery (M.D.)

1952-1953 = Military services
Present military position = Captain of Sanitary Service (in discharge)

1952-1954 = Assistant at the First-Aid Ward of the Milan Main General Hospital (Ospedale Maggiore)

= Assistant of the Medical Division "Carati" of the Milan Main General Hospital (Ospedale Maggiore)

1954-1955 = Assistant at the Cardiology Section of the Milan Municipality

1954-1956 = Assistant at the Neuropsychiatric Division "Origgi" of the Milan Main General Hospital (Ospedale Maggiore)

1956 = Specialization in Cardiology, University of Pavia

= Assistant at the Institute of Pharmacology of the University of Milan

1958 = Professoral postgraduation (Libera Docenza) in Pharmacology

= Assistant Professor of the Institute of Pharmacology of the University of Milan

1963 = till now: Chief, Section of Neuropsychopharmacology and Psychophysiology of the Institute for Pharmacological Research "Mario Negri" of Milan (via Eritrea 62, 20157 Milano, Italy)

1968 = till now: Teacher Professor of Psychophysiology and Psychopharmacology of the School of Specialization in Psychology of the University of Milan

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1971 = till now: Adjunct Professor of Psychology at the Queens College of the City University of New York

1971-1972 = Adjunct Professor at the University of Turin for the teaching of Psychophysiology and Psychopharmacology.

He speaks and writes English, French and Spanish.

Quoted = in WHO WHO'S IN EUROPE (since 1966; 2nd Edition)

in INTERNATIONAL DIRECTORY OF INVESTIGATORS IN PSYCHOPHARMACOLOGY (1972; p. 199)

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2. TEACHING ACTIVITIES

1960-1963 = Course of lessons on the Pharmacology of the Central Nervous System at the Medical Faculty of the University of Milan

1963 = (September); Member of the Teaching Staff of the 1st International Course on Spectrofluorimetry (held at the Institute for Pharmacological Research "Mario Negri" - Milan)

1965-1970 = Annual Course in Pharmacology for the students of the "Scuola per Laboratoristi Biologi" (held at the Institute for Pharmacological Research "Mario Negri" - Milan)

1966 = (March); Series of lessons during the 1st Course of Psychopharmacology for Practitioners (held at the Institute for Pharmacological Research "Mario Negri" - Milan)

= (September); Lesson during the 1st Course of Instrumentation for Laboratories of BioMedical Research (held at the Instituete for Pharmacological Research "Mario Negri" - Milan)

1968 = (February); Lesson during the 2nd Course of Instrumentation for Laboratories of BioMedical Research (held at the Institute for Pharmacological Research "Mario Negri" - Milan)

(March); Series of Lessons during the 2nd Course of Neuropsychopharmacology for Practitioners (held at the Institute for Pharmacological Research "Mario Negri" - Milan)

1968-1971 = Annual Course on Psychophysiology for the Postgraduated in Psychology of the University of Milan

1971 = (March); Visiting Professor at the Department of Psychology at the Queens College of the City University of New York

(May); Lesson at the Institute of Pharmacology of the University of Milan

(June); Lesson during the "Corso di aggiornamento in Neuropsicofarmacologia", held by Societ$ Italiana di Neuropsicofarmacologia, Milan

1972 = (January); Lesson during the Course organized by the European Training Program in Brain and Behaviour Research at Zuoz on "Transmission and behaviour"

(February); Lesson at Centro di Pronto Intervento Neuropsichiatrico "R. Bozzi", Milan

(March) Lesson at the Institute of Veterinary of the Faculty of Medicine of the University of Milan

1972-1973 =(April) Course of lessons in Experimental Psychology at the Department of Advanced Psychology of the Queens College of the City University of New York

1972 =(June); Lesson at the Psychiatric Clinic, University of Turin.

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3. CONGRESSES

1956 =	(speaker)	20th International Congress of Physiology, Bruxelles
1957 =	(speaker)	International Congress on "Psychotropic Drugs", Milan
1959 =	(speaker)	Symposium on "Pharmaka mit Wirkung auf den Monoaminstoffwechsel des Zentralnervensystem", Bad Nauheim
1960 =	(speaker)	Symposium on "Sindromi Depressive", Rapallo
	(speaker)	Symposium on "Spettrofotofluorimetria", Milan
1961 =	(speaker)	Symposium on "Monoamines et Systhème Nerveux Centrale", Genève
1963 =	(speaker)	1st International Course on Spectrophotofluorimetry, Milan
1966 =	(speaker)	5th International C.I.N.P. Symposium, Washington
	(speaker)	International Symposium on "Antidepressant Drugs", Milan
	(speaker)	Winter Meeting of the American Society of Zoologist, Washington
1967 =	(speaker)	International Symposium on "Biological role of Indolealkylamine derivatives", New York
	(speaker)	XIV Congresso Nazionale della Società Italiana di Farmacologia, Trieste
1968 =	(speaker)	International Symposium on "Quimioterapia de larga duracion en psiquiatria", Sitges (Barcelona)
	(speaker)	6th International C.I.N.P. Symposium, Tarragona
	(speaker-organizer)	1st International Congress on "Aggressive Behavior" Milan
	(speaker)	International Meeting of the Italian and British Societies of Pharmacology, Florence
	(speaker)	Table Ronde sur la Sérotonine et Pathologie Digestive, Vichy
	(speaker)	1st International Congress of the Collegium Internationale Activitas Nervosae Superioris (C.I.N.S.), Milan
1969 =	(chairman)	International Symposium on "Amphetamines and related compounds", Milan

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(speaker) II Riunione Nazionale della Società Italiana di Neuropsicofarmacologia, Tirrenia (Pisa)

(speaker) IV International Congress on Pharmacology, Basel

(organizer-chairman) Round Table on "Correlation between behaviour and transmitters (suspects) in brain", during the 2nd International Meeting of the International Society for Neurochemistry, Milan

(speaker) Round Table on "Serotonina in Patologia Umana", Fondazione C. Erba, Milan

(speaker) XV Congress of the Società Italiana di Farmacologia, Milan

(speaker) 2nd International Congress of the Polish Pharmacological Society, Warsaw

(speaker) 1st Interdisciplinary Meeting of Psychobiology, Parma

(organizer) 2nd Interdisciplinary Meeting of Psychobiology, Milan

(speaker) Round Table on Learning, Como

1970 = (speaker) Meeting of Gerontology, Milan

(speaker) Round Table on "Ipnosi, mezzi farmacologici e libertà individuale", Fondazione C. Erba, Milan

(speaker) Round Table on "Orientamenti attuali sul trattamento della malattia di Parkison", Fondazione C. Erba, Milan

(speaker) Round Table on "Psychotomimetic drugs", Varese

(speaker) Round Table on "I giovani e la droga", Fondazione C. Erba, Milan

(speaker) Congress on "Atherosclerosis and Central Nervous System", Fondazione C. Erba, Milan

(speaker) 3rd Interdisciplinary Meeting on Psychobiology on "Genetica e ambiente nel determinismo del comportamento degli animali e dell'uomo", Pavia

(speaker) International Symposium on "Migraine and headache", Florence

(speaker) Congress on "Malformazioni, tumori, difetti mentali e correlazioni patogenetiche", Fondazione C. Erba, Milan

(speaker) 3rd Meeting of the Società Italiana di Neuropsicofarmacologia on "Farmacoterapia della schizofrenia", Milan

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(speaker) Round Table on Psychotomimetic Drugs, Gallarate

(speaker) Meeting on Neurobiology, Rome

(chairman) NATO Course on Chemistry of Brain Development, Milano

(speaker) 39th Meeting of "Unione Zoologica Italiana", Salice Terme (Pavia)

(speaker) Round Table on "Associazioni Psicofarmacologiche" Società Italiana di Neuropsicofarmacologia Castelvecchio Pascoli, (Lucca)

(speaker) Workshop of the European Training Program in Brain and Behaviour Research, Milan

1971 - (speaker) Meeting at Istituto Carlo Erba, Milan

(speaker) Round Table on "Droghe e Minidroghe", Fondazione C. Erba, Milan

(Honor guest) Congress on "Monoamineoxidases: New Vistas" Cagliari

(chairman) Congress on "Physiology and Pharmacology of Cyclic AMP", Milan

(speaker-chairman) Joint Meeting of the Italian Pharmacological Society and the Belgian Physiological and Pharmacological Society, Gent - Belgium.

(speaker) Round Table on "Antiaggression" during the "International Symposium on Benzodiazepines", Milan

1972 - (speaker) Round Table on "Crisi dei giovani, droga, educazione" Fondazione C. Erba, Milan

(speaker) Federation Meetings, Atlantic City

(speaker) Neurophysiology Group Meeting on "Brain lesions and drug action", Atlantic City

(speaker) Workshop on Recent Advances in the "Psychobiology of Electroconvulsive Therapy", Puerto Rico

(speaker) Meeting on Learning and Memory, Ministero Pubblica Istruzione, Como

(chairman) Corso di aggiornamento in neuropsicopharmacologia on "Farmaci attivi sulle insonnie", Milan

(speaker) International Symposium on "Metabolic regulation and functional activity in the Central Nervous System" Saint Vincent

(speaker) Meeting on "Recenti sviluppi nella psicologia dell'apprendimento", Frascati

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4. LECTURES

1967 = (April); "Biochemical aspects and clinical implications of aggressive behaviour"; Endo Laboratories Inc., Garden City, New York

(May); "Comportamiento agressivo: fechas bioquimicas y farmacologicas"; Institute of Pharmacology, University of Barcelona

(November); "Biochemical and behavioural aspects of aggressiveness"; J.R. Geigy S.A., Basel

(December); "L'aggressività sperimentale", Psychiatric Clinic of the University of Genoa

1968 = (March); During the 2nd Course of Neuropsychopharmacology for Practitioners at the Institute for Pharmacological Research "Mario Negri", Milan

(April); "Antidepressant drugs", Institute of Pharmacology, University of Cagliari

(November): "Experimental aggressiveness: psychological, methodological, biochemical and pharmacological aspects"; Department of Pharmacology, Karolinska Institutet of Stockholm

1969 = (October); "Some aspects of induced aggressiveness in mice and rats" Department of Pharmacology, Medical Academy of Warsaw

1970 = (June); "Anticipazione dell'apprendimento e strutture cerebrali"; Ministero della Pubblica Istruzione

(November); "Nuove correnti scientifiche di trattamento medico-pedagogico del minorato" Società Italiana per l'Assistenza Medico-Psico-Pedagogica ai minorati dell'età evolutiva (SIAME), Sanremo

(November); "Memory mechanisms"; Clinica delle Malattie Nervose e Mentali, University of Rome

(November): "Memory mechanisms"; Clinica delle Malattie Nervose e Mentali, University of Siena

(November); "Sperimentazione e ricerche comprovanti il valore di alcuni fattori indispensabili allo sviluppo delle capacità di apprendimento"; Ministero della Pubblica Istruzione, Luino

(November); "Il problema del sonno"; Clinica Psichiatrica dell'Università di Verona

(December); "Aspetti psicosociali della droga"; PRO-FAR-BER, Bergamo

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1971 = (March); " Intéraction entre état émotif et activité des substances psychoactives" Unité de Neuropharmacologie, Paris

(March); "Agressivité chez le rat et la souris: aspects comportementaux et biochimiques"; Medical Faculty of Paris, (Actualités pharmacologiques)

(March); "Lesion and stimulation of brain structures as a tool to study mechanisms of drug action"; National Institutes of Mental Health, Saint Elizabeth's Hospital, William A. White Building, Washington D.C.

(April); "Neurochemistry of the Central Nervous System"; Centro di Pronto Intervento Neuropsichiatrico "R. Bozzi", Milan

(April); "Neurochemical correlates of behaviour"; Centro di Pronto Intervento Neuropsichiatrico "R. Bozzi", Milan

(May); "Substrato emotivo come condizionante l'attività degli psicofarmaci"; Clinica Psichiatrica dell'Università di Pavia

(October); "Aggressive behaviour: psychophysiological substrates, environmental influences, neurochemical aspects"; Clinica Psichiatrica, Università di Genova

1972 = (March); Seminar on "Aspetti psicosociali della droga" at Lions' Club of Mariano-Comense (Como, Italy)

(April); "Some biochemical and behavioral correlates of induced aggressiveness"; Columbia University, New York

(April); "Aggressiveness by isolation in mice and rats: behavioral and pharmacological aspects"; Temple University, Department of Pharmacology, Philadelphia.

(April); "Aggressiveness by isolation and drug effects: some biochemical and behavioral correlates of induced aggression"; Shering Corporation, Bloomfield, N.J.

(April); "Behavioral and neurochemical aspects of aggressiveness"; University of Connecticut, Dpt. Biobehavioral sciences, Storrs

(April); "Emotional modulation of psychotropic drugs"; University of Connecticut, Dpt. Biobehavioral sciences, Storrs

(May); "Lésions ou stimulations des voies monoaminergiques centrales et activité de quelques substances"; Centre National de la Recherche Scientifique, Centre de Neurochimie, Strasbourg

(May); "Aspect comportementaux, biochimiques et pharmacologiques de l'agressivité par isolement dans la souris et le rat"; Centre National de la Recherche Scientifique, Centre de Neurochimie, Strasbourg

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5. RESEARCH GRANTS

1963 = "Isolation of physiological active substances from brain"
U.S.A. Army contract n. DA-91-591-EUC-2687 - with S. Garattini

1964 = "Isolation of physiological active substances from brain"
U.S.A. Army contract n. DA-91-591-EUC-3234 - with S. Garattini

1966 = "Pharmacological and biochemical changes in animals made aggressive by isolation"
U.S.A. Army contract n. DA-91-591-EUC-4058 - with S. Garattini

1967 = "Pharmacological and biochemical changes in animals made aggressive by isolation"
U.S.A. Army contract n. DAJA-37-67-C-0586 - with S. Garattini

= "Effect of drugs on age and behavior"
National Institutes of Health, Bethesda, Md., U.S.A., contract n. DHEW/PHS/NIH PH-43-67-83 - with S. Garattini

1968 = "Pharmacological and biochemical changes in animals made aggressive by isolation"
U.S.A. Army contract n. DAJA-37-68-C-1076 - with S. Garattini

= "Effect of drugs on age and behavior"
National Institues of Health, Bethesda, Md., U.S.A.
contract n. DHEW/PHS/NIH PH-43-67-83 - with S. Garattini

1969 = "Effect of drugs on age and behavior"
National Institutes of Health, Bethesda, Md., U.S.A.
contract n. DHEW/PHS/NIH PH-43-67-83 - with S. Garattini

"Activité du Sulpiride (Dogmatil) sur les activités nerveuses superieures"
Laboratoires Delagrange, Paris

1970 = "Activité du Sulpiride (Dogmatil) sur les activités nerveuses superieures"
Laboratoires Delagrange, Paris

"Aspetti farmacologici e biochimici della aggressività sperimentale da isolamento"
C.N.R. (Centro Nazionale della Ricerca, Roma), contract n. 70.01143.04

1971 = "Aspetti farmacologici e biochimici della aggressività sperimentale da isolamento"
C.N.R. (Centro Nazionale della Ricerca, Roma), contract n. 70.01143.04

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1971 = "Attività della Caffeina sul Sistema Nervoso Centrale"
Crippa & Berger, Milan.

1971-1972= "Study on the comparative pharmacology of steroid contraceptive drugs"
National Institute of Child Health and Human Development, U.S.A.

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6. MEMBERSHIPS

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Correspondent Member of the Journal "Bulletin de Recherches Thérapeutiques".

Referee for Psychopharmacology of the "European Journal of Pharmacology", and "Pharmacological Research Communications".

7. AWARDS

1968 = "Ambrogino d'oro" from the Comune of Milano for the contribution as organizer of the 1st International Congress on "Aggressive Behaviour" (Milan, 1968).

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8. BOOKS

1965 = "Serotonin", with S. Garattini
Elsevier Publishing Company, Amsterdam

1967 = contributor to "Advances in Pharmacology", vol.5, Academic Press Inc., New York

1970 = contributor with S. Garattini to the volume "Principles of Psychopharmacology" (W.G. Clark and J. Del Giudice, eds.) Academic Press Inc., New York

italian translation of the volume "Clinical Psychopharmacology" by M. Shepherd, M. Lader and R. Rodnight (C.Manfredi, Milan)

"Elementi di Psicofarmacologia, Sperimentale e Clinica" C. Manfredi, Milan

1971 = "Profili di Psicofisiologia e Neurochimica" C. Manfredi, Milan

1973 = "Psychopharmacology: an introduction to experimental and clinical principles"
Spectrum Publications, New York, W.B. Essman editor.

9. PUBLICATIONS

October 1972 = 120 published papers and 8 papers in press.

See the enclosed list.

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(3)

ELENCO DEI

LAVORI PUBBLICATI

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tonin after electrical shock"
L. Valzelli (in collaborazione con S. Garattini e A. Valsecchi)
Experientia, 13 (1957) 330

18 — "Serotonin and electroshock"
L. Valzelli (in collaborazione con S. Garattini)
Atti del Congresso Internazionale sui Farmaci Psicotropi (Milano, 1957)
Eds. S. Garattini & V. Ghetti - Elsevier Publ. Co., Amsterdam, pag. 435

19 — "Azione della veratrina sul contenuto in serotonina del cervello e dell'intestino di ratto"
L. Valzelli (in collaborazione con A. Bertelli)
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L. Valzelli (in collaborazione con S. Garattini)
Boll.Soc.It.Biol.Sper., 32 (1956) 288

6 — "Sostanze interferenti sull'attività antidiuretica svolta dalla serotonina"

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L. Valzelli (in collaborazione con S. Garattini)
Boll.Soc.It.Biol.Sper., 32 (1956) 295

7 — "Sostanze interferenti sull'attività potenziante gli ipnotici svolta dalla serotonina"
L. Valzelli (in collaborazione con S. Garattini)
Boll.Soc.It.Biol.Sper., 32 (1956) 292

8 — "Tassi di lipidi e colesterolo nel tessuto miocardico e aortico di soggetti umani venuti a morte"
L. Valzelli
Folia Cardiologica, 15 (1956) 551

9 — "Effect of some substances on serotonin activity"
L. Valzelli (in collaborazione con S. Garattini)
Atti del XX Congresso Internazionale di Fisiologia (Bruxelles, 1956)

10 — "Reserpina elettroshock e serotonina encefalica"
L. Valzelli (in collaborazione con B. Murelli e A. Valsecchi)
Boll.Soc.It.Biol.Sper., 33 (1957) 859

11 — "Alcune attività dell'1-benzil-2-metil-5-metossitriptamina (BAS) sul sistema nervoso centrale"
L. Valzelli (in collaborazione con B. Murelli e A. Valsecchi)

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Boll.Soc.It.Biol.Sper., 33 (1957) 863

12 — "Sulle attività di una molecola antiserotoninica: l'1-benzil-2-metil-5-metossitriptamina (BAS) su alcuni organi isolati e sulla diuresi"
L. Valzelli (in collaborazione con B. Murelli e A. Valsecchi)
Boll.Soc.It.Biol.Sper., 33 (1957) 859

13 — "Il potenziamento della narcosi da barbiturici dopo elettroshock"
L. Valzelli (in collaborazione con A. Jori e A. Valsecchi)
Boll.Soc.It.Biol.Sper., 33 (1957) 854

14 — "Elettroshock, serotonina ed eliminazione urinaria"
L. Valzelli (in collaborazione con A. Valsecchi)
Boll.Soc.It.Biol.Sper., 33 (1957) 855

15 — "Variazioni nel contenuto della serotonina encefalica in differenti specie animali dopo elettroshock"
L. Valzelli (in collaborazione con P. Fresia, E. Genovese e A. Valsecchi)
Boll.Soc.It.Biol.Sper., 33 (1957) 888

16 — "Convulsioni e serotonina encefalica"
L. Valzelli (in collaborazione con A. Jori e A. Valsecchi)
Boll.Soc.It.Biol.Sper., 33 (1957) 921

17 — "Variations in encephalic intestinal sero

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ENCLOSURE (D)

(4)

Prof. EMILIO MUSSINI

CURRICULUM VITAE

October 1972

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R: REDACTED MATERIAL

1. BIOGRAPHICAL SKETCH

Name = MUSSINI Emilio

Present Position = Chief, Section of Biochemical Pharmacology of the Istituto di Ricerche Farmacologiche "Mario Negri", Milan Italy

REDACTED

= Student at the Faculty of Medicine and Surgery, University of Modena

REDACTED = Internal Student, Institute of General Pathology

= Internal Student, Institute of Medical Pathology

= Graduated in Medicine and Surgery (M.D.) at the University of Milan

1953-1954 = Assistant, Institute of Clinical Medicine, University of Milan

= Assistant, Institute of Pharmacology, University of Milan

1954 = Fellowship, Pasteur Institute, Paris

1954-1958 = Special Assistant, Institute of Pharmacology, University of Milan

1958-1959 = Assistant in charge, Institute of Pharmacology, University of Milan

1959 = Professoral Postgraduation (Libera Docenza) in Pharmacology

1959-1963 = Assistant Professor, Institute of Pharmacology, University of Milan

1961 = Visiting Scientist at City of Hope, Duarte, Calif.

1963 = to date: Chief Section of Biochemical Pharmacology of the Istituto di Ricerche Farmacologiche "Mario Negri" - Via Eritrea 62, 20157 Milan, Italy

1966 = Visiting Scientist, National Institutes of Health, Bethesda, Md., Section of Clinical Biochemistry

1970 = Member of the Council for Biomedical Technology of the "Centro Nazionale delle Ricerche" (C.N.R.).

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He speaks and writes Eglish and French.

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2. TEACHING ACTIVITY

1955-1963 = Courses of Lessons for Medical Students at the Medical Faculty of the University of Milan.

1963 = (September); Member of the teaching staff of the 1st International Course on Spectrofluorometry (held by the Istituto di Ricerche Farmacologiche "Mario Negri", Milan)

1966 = (March); Member of the teaching staff of the 1st Course of Psychopharmacology for Practitioners (held by the Istituto di Ricerche Farmacologiche "Mario Negri", Milan)

= (September); Lesson during the 1st Course of Instrumentation for Laboratories of BioMedical Research (held by the Istituto di Ricerche Farmacologiche "Mario Negri", Milan)

1968 = (February); Lesson during the 2nd Course of Instrumentation for Laboratories of BioMedical Research (held by the Istituto di Ricerche Farmacologiche "Mario Negri", Milan)

(March); Member of the teaching staff of the 2nd Course of Neuropsychopharmacology for Practitioners (held by the Istituto di Ricerche Farmacologiche "Mario Negri, Milan)

1970 = (May) Lesson on Gas Chromatography at the Course on Instrumentation for Laboratories of BioMedical Research (held by the Istituto di Ricerche Farmacologiche "Mario Negri", Milan).

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3. CONGRESSES

1963 = (Speaker) at the "International Course on Spectrophotofluorometric techniques in biology", Milan

1964 = (Speaker) at the "International Symposium on non-steroidal anti-inflammatory drugs", Milan

1965 = (Speaker) at the Technicon Symposium in Paris

(Speaker) at the Technicon Symposium in London

(Speaker) at the Technicon Symposium in Frankfurt

(Speaker) at the Technicon Symposium in Rome

1966 = (Speaker) at the 2° Symposium Mario Negri, Milan

1967 = (Speaker) at the 3° Symposium Mario Negri, Milan

1968 = (Speaker) at the 4° Symposium Mario Negri, Milan

1969 = (Speaker) at the 5° Symposium Mario Negri, Milan

1971 = (Speaker) at the "International Symposium on Benzodiazepines", Milan.

4. LECTURES

1961 = Lectures on "Aminoacids in the rat brain after treatment with psychotropic drugs" at City of Hope, Duarte, Calif.

1965 = Lectures on gas-chromatography techniques at the Symposiums held by Technicon in Paris, London, Frankfurt and Rome

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5. RESEARCH GRANTS

1963 = "Isolation of physiologically active substances from brain"
U.S.A. Army contract n. DA-91-591-EUC-2687 - with S. Garattini

1964 = "Isolation of physiologically active substances from brain"
U.S.A. Army contract n. DA-91-591-EUC-3234 - with S. Garattini

1965-1969 = "A study on the mechanism of gossypol toxicity counteraction by L-Lysine, to gain information needed to permit the increased use of cottonseed products in animal feeds"
Fg-It-131 contract, - with S. Garattini

1970-1971 = Programma Speciale "Tecnologie Biomediche"
C.N.R. Contract n. 70.00716/31-17-9-3 - with S. Garattini

1971-1972 = "Study on the comparative pharmacology of steroid contraceptive drugs"
National Institute of Child Health and Human Development, U.S.A., contract n. NIH-NICDH-72-2733 - with S. Garattini

Programma Speciale "Tecnologie Biomediche; Tossicità dei Farmaci"
C.N.R. Contract n. 70.00716/31-17-9.3 - with S. Garattini

6. MEMBERSHIPS

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Referee of the "European Journal of Pharmacology."

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7. PUBLICATIONS

October 1972 = 68 published papers and 3 papers in press (see enclosed list).

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LIST OF PUBLICATIONS

1. Garattini S., Mussini E.: Fegato in degenerazione grassa ed inibizione di sue attività a tipo disulfurasico. Atti Soc. Lomb. Sci. Med. Biol., 1953, 8, 444.

2. Bassoli G., Benati E., Mussini E.: Cortisone, ormone somatotropo, gruppi sulfidrilici del fegato e reazione cutanea alla tubercolina. Giorn. It. Chemioter., 1954, 1, 539.

3. De Poli A., Mussini E.: Titolazione amperometrica dei gruppi sulfidrilici nel cristallino catarroso. Atti Soc. Oftalmol. Lomb., 1954, II.

4. Garattini S., Mussini E.: Sulla distribuzione degli SH nell'organismo. Atti Soc. Lomb. Sci. Med. Biol., 1954, 9, 125.

5. Garattini S., Mussini E.: Ricerche sul meccanismo dell'azione diuretica dei mercuriali. Atti Soc. Lomb. Sci. Med. Biol., 1954, 9, 131.

6. Garattini S, Mussini E.: Sui rapporti tra ATP e gruppi sulfidrilici. Boll. Soc. It. Biol. Sper., 1954, 30, 1114.

7. Garattini S., Mussini E.: Sul contenuto in gruppi sulfidrilici nel fegato dopo trattamento con aminoacidi solforati. Boll. Soc. It. Biol. Sper., 1954, 30, 1117.

8. Garattini S., Mussini E.: Aumento di gruppi sulfidrilici nell'ipofisi durante la gravidanza. Boll. Soc. It. Biol. Sper., 1954, 30, 1119.

9. Garattini S., Mussini E., Paoletti R.: Sulla possibilità di antagonizzare gli effetti tossici dell'isoniazide (INI). Giorn. It. Chemioter., 1954, 1, 262.

10. Bassoli G., Mussini E.: Sul comportamento delle proteine e dei gruppi sulfidrilici in rapporto con la gravità della malattia tubercolare. Giorn. It. Chemioter., 1955, 2, 83.

11. Bertelli A., Mussini E.: Azione della strofantina sui gruppi-SH del cuore. Boll. Soc. It. Biol. Sper., 1955, 31, 1168.

12. Cocucci M., Garattini S., Mussini E.: Sul comportamento di gruppi sulfidrilici del fegato dopo trattamento con cortisone, idrocortisone, metacortandracin. Boll. Soc. It. Biol. Sper., 1955, 31, 850.

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13. Ferri L., Mussini E., Palazzi D.: Gruppi sulfidrilici nel sarcoma 180 del topo e nell'adenocarcinoma di Walker del ratto dopo irradiazione. Tumori, 1955, 29, 424.

14. Garattini S., Mussini E.: Separazione cromatografica su carta di alcune purine (6-mercaptopurina, tioguanina, adenina e guanina). Boll. Soc. It. Biol. Sper., 1955, 31, 870.

15. Bizzi L., Murelli B., Mussini E.: Rame e sue diverse fissazioni al siero ed ai tessuti nel ratto e nella cavia. Arch. E. Maragliano, 1957, 13, 1.

16. Leonardi A., Mussini E.: Aminoacidi presenti nel siero dopo trattamento cortisonico in animali normali e surrenectomizzati. Giorn. It. Chemioter., 1958, 5, 179.

17. Marcucci F., Mussini E.: Diminuizione della eliminazione urinaria di taurina dopo trattamento prolungato con isoniazide. Boll. Soc. It. Biol. Sper., 1958, 34, 1103.

18. Marcucci F., Mussini E.: Diminuizione della eliminazione biliare di acido taurocolico dopo trattamento prolungato con isoniazide. Boll. Soc. It. Biol. Sper., 1958, 34, 1104.

19. Marcucci F., Mussini E.: Sulla eliminazione di acido cisteico e di taurina dopo trattamento con isoniazide Boll. Soc. It. Biol. Sper., 1958, 34, 1422.

20. Marcucci F., Mussini E.: Metabolismo degli aminoacidi solforati in animali trattati cronicamente con idrazide isonicotinica. Giorn. It. Chemioter., 1958, 5, 183.

21. Mussini E.; Sulla distribuzione nell'organismo e sull'attività diuretica dei p-cloro mercuri-benzoato. Boll. Soc. It. Biol. Sper., 1958, 34, 1586.

22. Mussini E.: Nuovo rapido metodo di dosaggio dei gruppi sulfidrilici in materiali biologici. Boll. Soc. It. Biol. Sper., 1958, 34, 1419.

23. Mussini E.: Distribuzione dei diuretici mercuriali nell'organismo. Boll. Soc. It. Biol. Sper., 1958, 34, 1487.

24. Mussini E.: Sui legami dei diuretici mercuriali alle proteine del siero. Boll. Soc. It. Biol. Sper., 1958, 34, 1588.

25. Mussini E.: Sulla distribuzione nell'organismo o sulla attività diuretica del p-cloro-mercuri-benzoato. Boll. Soc. It. Biol. Sper., 1958, 34, 1586.

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26. Mussini E.: Mancato effetto dell'isoniazide sul contenuto urinario di guanidotaurina e carbamiltaurina. Atti Soc. Lomb. Sci. Med. Biol., 1958, 3, 212.

27. Mussini E.: Aminoacidi presenti nel siero dopo trattamento cortisonico in animali normali e surrenectomizzati. Giorn. It. Chemioter., 1958, 5, 77.

28. Mussini E., Valzelli L.: Sostanze idoliche presenti nelle banane e modificazioni nel ricambio indolico in rapporto a diete a base di banane. Atti Soc. Lomb. Sci. Med. Biol., 1958, 13, 310.

29. Mussini E., Valzelli L.: Effetto precipitante svolto dal rame su sieri provenienti da diverse specie animali. Boll. Soc. It. Biol. Sper., 1958, 34, 1438.

30. Marcucci F., Mussini E.: A new apparatus for thin-layer chromatography. J. Chromatogr., 1963, 11, 270.

31. Marcucci F., Mussini E.: Separation of proline and hydroxyproline derivatives by thin-layer chromatography. J. Chromatogr., 1965, 18, 431.

32. Marcucci F., Mussini E., Poy F., Gagliardi P.: Separation of amino acids as their N-trifluoroacetyl-n-butyl esters by gas chromatography. J. Chromatogr., 1965, 18, 487.

33. Mussini E., Marcucci F.: Separation of prolines and hydroxyprolines by gas chromatography. J. Chromatogr., 1965, 20, 266.

34. Mussini E., Marcucci F.: Separation of amino acid n-butyl esters by means of thin-layer chromatography. J. Chromatogr., 1965, 17, 576.

35. Marcucci F., Mussini E.: A method for the gas-chromatographic analysis of n-acetyl-aspartic acid in brain. J. Chromatogr., 1966, 25, 11.

36. Marcucci F., Mussini E., Valzelli L., Garattini S.: Distribution of N-acetyl-L-aspartic acid in rat brain. J. Neurochem., 1966, 13, 1069.

37. Mussini E., Hutton J.J.Jr., Udenfriend S.: Collagen proline hydroxylase in wound healing, granuloma formation, scurvy, and growth. Science, 1967, 157, 927.

38. Mussini E., Marcucci F.: The preparation of diazopropane and diazobutane for the esterification of amino acids. J. Chromatogr., 1967, 26, 481.

39. Mussini E., Marcucci F., Garattini S.: Postnatal changes in brain N-acetyl-L-aspartic acid content of normal and hypothyroid suckling rats. J. Neurochem., 1967, 14, 551.

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40. Marcucci F., Fanelli R., Mussini E.: A method for gas-chromatographic determination of benzodiazepines. J. Chromatogr., 1968, 37, 318.

41. Marcucci F., Cuaitani A., Kvetina J., Mussini E., Garattini S.: Species differences in diazepam metabolism and anticonvulsant effect. Europ. J. Pharmacol., 1968, 4, 467.

42. Marcucci F., Mussini E.: A metabolic explanation for differences between species of the anticonvulsant activity of diazepam. Brit. J. Pharmacol., 1968, 34, 667P.

43. Marcucci F., Mussini E., Valzelli L., Garattini S.: Decrease in N-acetyl-L-aspartic acid in brain of aggressive mice. J. Neurochem., 1968, 15, 53.

44. Morselli P.L., Garattini S., Marcucci F., Mussini E., Rewerski W., Valzelli L., Peters R.A.: The effect of injections of fluorocitrate into the brains of rats. Biochem. Pharmacol., 1968, 17, 195.

45. Bartosek I., Mussini E., Garattini S.: Reduction of nitrazepam by rat liver. Biochem. Pharmacol., 1969, 18, 2263.

46. Garattini S., Marcucci F., Mussini E.: Gas chromatographic analysis of benzodiazepines. In "Gas chromatography in Biology and Medicine", Porter R. ed., J.A. Churchill Ltd., London, 1969, p.161.

47. Marcucci F., Airoldi L., Mussini E.: Brain level of N-acetyl-L-aspartate in different strains of mouse and rat. J. Neurochem., 1969, 16, 272.

48. Marcucci F., Fanelli R., Mussini E., Garattini S.: The metabolism of diazepam by liver microsomal enzymes of rats and mice. Europ. J. Pharmacol., 1969, 7, 307.

49. Bartosek I., Mussini E., Saronio C., Garattini S.: Studies on nitrazepam reduction "in vitro". Europ. J. Pharmacol., 1970, 11, 249.

50. Garattini S., Marcucci F., Mussini E.: Studies on the anticonvulsant action of diazepam. Brit. J. Pharmacol., 1970, 38, 455P.

51. Marcucci F., Fanelli R., Mussini E., Garattini S.: Effect of phenobarbital on the "in vitro" metabolism of diazepam in several animal species. Biochem. Pharmacol., 1970, 19, 1771.

52. Marcucci F., Fanelli R., Mussini E., Garattini S.: Further studies on species difference in diazepam metabolism. Europ. J. Pharmacol., 1970, 9, 253.

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53. Marcucci F., Fanelli R., Mussini E., Garattini S.: Further studies on the long lasting antimetrazol activity of diazepam in mice. Europ. J. Pharmacol., 1970, 11, 115.

54. Marcucci F., Mussini E., Fanelli R., Garattini S.: Species differences in diazepam metabolism. I. Metabolism of diazepam metabolites. Biochem. Pharmacol., 1970, 19, 1847.

55. Marcucci F., Mussini E., Morselli P.L., Garattini S., Libretti A., Zaccala M.: Osservazioni sul metabolismo delle benzodiazepine nell'uomo. In "Atti 2° Riunione Nazionale della Società Italiana di Neuropsicofarmacologia", Tirrenia, 1969, Arti Grafiche Pacini e Mariotti, Pisa, 1970, p.63.

56. Forgione A., Martelli P., Marcucci F., Fanelli R., Mussini E., Jommi G.C.: Gas liquid chromatography and mass spectrometry of various benzodiazepines. J. Chromatogr., 1971, 59, 163.

57. Marcucci F., Airoldi L., Mussini E., Garattini S.: A method for gas chromatographic determination of butyrophenones. J. Chromatogr., 1971, 59, 174.

58. Marcucci F., Airoldi M.L., Mussini E., Garattini S.: Brain level of metrazol determined with a new gas chromatographic procedure. Europ. J. Pharmacol., 1971, 16, 219.

59. Marcucci F., Guaitani A., Fanelli R., Mussini E., Garattini S.: Metabolism and anticonvulsant activity of diazepam in guinea pigs. Biochem. Pharmacol., 1971, 20, 1711.

60. Marcucci F., Mussini E., Airoldi L., Fanelli R., Frigerio A., De Nadai F., Bizzi A., Rizzo M., Morselli P.L., Garattini S.: Analytical and pharmacokinetic studies on butyrophenones. Clin. Chim. Acta, 1971, 34, 321.

61. Marcucci F., Mussini E., Guaitani A., Fanelli R., Garattini S.: Anticonvulsant activity and brain levels of diazepam and its metabolites in mice. Europ. J. Pharmacol., 1971, 16, 311.

62. Mussini E., Marcucci F., Fanelli R., Garattini S.: Metabolism od diazepam and its metabolites by guinea pig liver microsomes. Biochem. Pharmacol., 1971, 20, 2529.

63. Bertagni P., Marcucci F., Mussini E., Garattini S.: Biliary excretion of conjugated hydroxyl benzodiazepines after administration of several benzodiazepines to rats, guinea pigs, and mice. J. Pharm. Sci., 1972, 61, 965.

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64. Bizzi A., Tacconi M.T., Airoldi L., Marcucci F., Mussini E., Garattini S.: Haloperidol and trifluperidol in rat adipose tissue. Rev. Europ. Etud. Clin. Biol., 1972, 17, 169.

65. Marcucci F., Airoldi L., Mussini E., Garattini S.: Distribution of haloperidol and trifluperidol in brain and blood of rats. Chem.-Biol. Interactions, 1972, 4, 427.

66. Marcucci F., Mussini E., Airoldi L., Guaitani A., Garattini S.: Brain concentrations of lorazepam and oxazepam at equal degree of anticonvulsant activity. J. Pharm. Pharmacol., 1972, 24, 63.

67. Mussini E., Marcucci F., Fanelli R., Garattini S.: Metabolism of diazepam metabolites in guinea pigs. Chem.-Biol. Interactions, 1972, 5, 73.

68. Mussini E., Marcucci F., Fanelli R., Guaitani A., Garattini S.: Analytical and pharmacokinetic studies on the optic isomers of oxazepam succinate half-ester. Biochem. Pharmacol., 1972, 21, 127.

69. Garattini S., Marcucci F., Mussini E.: Benzodiazepine metabolism in vitro. Drug Metabolism Reviews, in press.

70. Garattini S., Marcucci F., Morselli P.L., Mussini E.: The Significance of measuring blood levels of benzodiazepines. In "The Benzodiazepines", Garattini S. and Randall L.O. eds., Raven Press, New York, 1973 in press.

71. Mussini E., Marcucci F., Airoldi L., Fanelli R., Morselli P.L., Garattini S.: Urinary excretion of C_3 hydroxylated benzodiazepines in man. Europ. J. Clin. Pharmacol., in press.

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